REMARKS

At the outset, Applicants and the undersigned wish to thank Examiners Friend and Venkat for the extremely helpful personal interview held on May 14, 2002. As was discussed during the interview, the invention, as now defined in the new, narrowed set of claims, features methods for performing high throughput screens of combinations of compounds on living test cells, to discover new combinations of compounds *that have potential therapeutic use in animals, particularly humans.* In the claimed methods, each compound of the new, therapeutically effective combination is tested individually on the test cells, to demonstrate that the new combination causes an effect on a biological property of the test cells that is superior to the effect of each of the compounds by itself. The methods of the invention can identify therapeutically effective combinations of compounds even where each compound of the combination may have previously had no known biological effect on cells of the type of the test cells, and even where the compounds would not have been obvious candidates to use in combination.

The Office Action

All of the previously pending claims have been non-finally rejected under 35 U.S.C. §§ 112 (first and second paragraphs) and 103. In addition, the disclosure of the specification was objected to on two grounds. Each rejection and objection is addressed below.

Objections to the Specification

The specification was objected to because of the presence of hyperlinks, and because of improper use of trademarks. These defects have been corrected in the substitute specification,

submitted herewith along with a marked-up version. This substitute specification contains no new matter. Applicants note that "fluo-3" is not a trademark.

Rejections Under 35 U.S.C. § 112, First Paragraph (written description and enablement/claim scope)

All of the pending claims were rejected on the ground that Applicants did not show, in the application, possession of "representative examples" of assays, cell types, biological activity, and compound combinations. All of the claims were also rejected for overbreadth, with the Office (citing *In re Wands*) asserting that the specification "does not reasonably provide enablement for any test compounds and any assay using any cell," because in the view of the Office such uses would require "undue experimentation."

With respect to these rejections (which are closely related and thus considered together herein), the Office acknowledges that the specification does in fact describe many examples in each category (compounds, assays, cells, and biological activity) but faults the application for not *demonstrating* sufficient numbers of them. These rejections are based on incorrect premises with respect to the requirements of the statute, and should be withdrawn.

Contrary to the main premise on which the rejections are based, the law does not require, for satisfaction of the written description and enablement requirements, that the specification *demonstrate* that numerous embodiments of the invention had been proven efficacious prior to the filing of the application. In fact, an important policy underlying the patent statute is the encouragement of the early filing, and thus disclosure, of an invention, before the invention has been optimized and repeatedly used. Applicants have carried out the claimed methods many (more than a million) times since filing the application, using a variety of assays and cell types, all of which are described, prophetically and in enabling detail, in the specification. No purpose

would have been served by postponing filing until these additional assays had been carried out, and indeed the public interest would have been ill served by such delay.

The Office Action notes that the claims encompass assays using "any compound," and asserts that the claims are therefore overbroad, as "(g)uidance is lacking ... with respect to the selection of compounds to be tested in any particular assay." The Office Action goes on to note that "the predictability of screening compounds randomly ... for synergy is very low."

The Office is correct in asserting that any compounds can be tested according to the methods of the invention. The Office is also correct that it is difficult (actually, it is impossible) to predict whether two randomly selected compounds will interact synergistically on a living cell. Neither fact is relevant to the patentability of the present claims. Applicants have provided ample guidance as to how the assays of the invention can be carried out. No "selection" of tested compounds is required; the methods do not depend on what compounds are being tested; they are the same for any test compound, whether it be a small molecule or a protein or a molecule having no known biological activity. The fact that the "hit" rate of synergistic combinations is necessarily low is also irrelevant: the methods of the invention use high throughput screening, capable of testing hundreds of thousands of combinations in a matter of days, using robots requiring little human supervision. Indeed, this point is conceded in the Office Action itself: "Screening of particular classes of compounds for specific biological functions was known in the art. The prior art provides large numbers of cell-based assays for [a] large variety of functional screens for many classes of compounds."

Thus it is uncontested that high throughput screening methods were known and are enabled by the specification, and that many different screening assays employed in those high throughput modes were also known. Furthermore, as was discussed during the interview, the

methods described in enabling detail in the specification have repeatedly been demonstrated, by Applicants, to produce precisely the results that are described in the specification: the discovery of numerous new therapeutically useful combinations of compounds. It does not follow from the fact that the therapeutically relevant biological activity of each of these combinations was "unexpected" that the disclosure is not enabling; while the *results* yielded by the claimed methods could not have been predicted (the methods would not have been needed had the results already been know), the *methods* used to produce those results are set out in great detail in the specification, which provides numerous, varied examples, almost all of which are based on materials and techniques that had already been well established in the prior art.

It is respectfully requested that the rejections under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejections Under 35 U.S.C. § 112, Second Paragraph (indefiniteness)

All of the claims were rejected for indefiniteness. Most of these rejections are met by the present amendments to the claims.

The error in claim 1 pointed out by the Office has been corrected by the elimination, in new claim 89, which replaces cancelled claim 1, of the "7x7 array" language; claim 89 simply requires the use of at least seven compounds in at least forty-nine combinations of compounds.

The Office points out, correctly, that the "effect" recited in step (f) of claim 1 (now step c) of claim 89) is written broadly enough to encompass both qualitative and quantitative differences. To ensure that there is no ambiguity, claim 89 now explicitly recites these two possibilities.

The linking error (Paragraph 6.C of the Office Action) has been corrected by the language of new claim 89.

The lack of clarity pointed out in Paragraph 6.D has been rectified by the language of new claim 89.

It is believed that the term "microfluidics" in prior claim 15 (now claim 100) needs no further definition. The term "microfluidics" is defined in the specification on page 10, lines 5-9:

> "'Microfluidics': As used herein, 'microfluidics' devices are channeled structures made by any of the methods of photolithography, including conventional photolithography (e.g. Caliper Technologies, Mountain View, CA; http://www.calipertech.com) or unconventional methods (such as soft lithography, described, e.g., in Angew. Chem. Int. Ed. Engl. 1998, 37, 550-575)."

The fact that microfluidics devices can be *made* by both conventional and unconventional methods does not render the term, which refers to a device, not a method, indefinite.

Applicants note the comments of the Office (Paragraph 6. F) regarding the claim term "synergistic." Applicants believe that this term does not violate § 112.

It is believed that the claims referred to in Paragraph 6. G are not ambiguous; the fact that they can encompass homogenous or heterogeneous test cell arrays conforms with the statute.

The Office asserts that the term "small molecule" is indefinite (Paragraph 6.H). In response, Applicants have replaced this language with "a molecule with a molecular weight of less than 1500 g/mole" in new claims 108-111, 122-132, 145-148, and 150-154. Support for this limitation is found in the specification on page 10, lines 12-17.

Rejection Under 35 U.S.C. § 103 (obviousness)

All of the claims were rejected for obviousness over a newly cited reference, Koller et al. (hereafter, "Koller"). In view of the new, narrower claims that have been substituted for the

prior claims, as well as the following comments, it is respectfully requested that the obviousness rejection be withdrawn.

At the outset, Applicants note that the Office's summary of the Koller experiments is accurate. The Koller experiments were conducted by scientists employed by Aastrom BioSciences, Inc., a company in the business of culturing stem cells for use in bone marrow transplantation. The primary purpose of the Koller experiments was to optimize the culture media in which the stem cells were grown. As the Office Action notes, Koller tested various combinations of growth factors (some of which are FDA-approved drugs such as EPO) which had been used by other groups of researchers growing stem cells, to determine which combination of factors worked best in stem cell culture media.

Koller, conceptually, has nothing to do with the invention, as now claimed in the replacement claim set. The claimed invention is directed to discovering new combinations of compounds that can be used as *therapeutics*, i.e., drugs for administration to animals, particularly humans. The prior claims, Applicants appreciated upon studying Koller, were too broad, in that they did not specify that the desired combinations of compounds are useful as therapeutics; the claims recited the broader term "biological activity." Of course, the Office is correct that Koller's combinations have biological activity, in that they promote the growth of stem cells in culture. This is not the sort of biological activity to which the present invention is directed, and therefore the new, narrower claims are limited to *therapeutic* combinations. The invention, as now claimed, would not have been obvious in view of Koller, and indeed a critical threshold point is that Koller is not even in the same field as the present invention, i.e., the field of drug discovery. Koller makes no mention of discovering drugs for administration to animals or humans, but rather is in the unrelated field of cell culture; there is no mention anywhere in Koller

of the discovery or administration of drugs. Thus Koller is "non-analogous art," and for this reason alone cannot form the basis for an obviousness rejection. See *In re Oetiker*, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992):

> "The combination of elements from non-analogous sources, in a manner that reconstructs the Applicant's invention only with the benefit of hindsight, is insufficient to present a *prima facie* case of obviousness."
>
> "We have reminded ourselves and the PTO that it is necessary to consider 'the reality of the circumstances,' *In re wood* 599 F.2d 1032, 1036, 202 USPQ 171, 174 (CCPA 1979) --in other words, common sense-- in deciding in which fields a person of ordinary skill would reasonably be expected to look for a solution to the problem facing the inventor."

and MPEP 2141.01(a):

> " In order to rely on a reference as a basis for rejection of an Applicant's invention, the reference must either be in the field of aApplicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned."

Accordingly, Koller is non-analogous art because drug development and cell culturing are entirely different endeavors with entirely different goals and because one interested in identifying new therapeutic agents would not look to the science of cell culturing for a solution.

Furthermore, and perhaps even more fundamentally, Koller teaches away from the invention, and thus bolsters, not undermines, patentability. Koller, ultimately, is concerned with human therapy, but *only by administering cells, not drugs.* Even if some of the combinations of compounds Koller used to grow cells could have been used as drugs in humans (which is extremely doubtful), such a fact would have been lost on Koller. Indeed, once the compound combinations of Koller had done their job of promoting the growth of stem cells, rather than being tested for efficacy on animals or humans to treat disease, *those combinations were washed*

down the drain. Koller is careful to note that the therapeutic product, stem cells, must be completely free of growth factors. Koller emphasizes the importance of "cell purity" (p.1785, col. 1), and repeatedly describes "washing" away the growth factors from the cells prior to their use (p. 1786, col. 1). No one of ordinary skill in the field of drug discovery would have conceived of Applicants' invention, as now claimed, based on Koller's discarding, rather than therapeutic use, of the Koller combinations.

Conclusion

Applicants submit that the claims are now in condition for allowance and such action is respectfully requested.

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Respectfully submitted,

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